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TITLE: *Conditioned Fear Extinction and Generalization in Post-Traumatic Stress Disorder*

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14. ABSTRACT

Post-traumatic stress disorder (PTSD) can affect an individual following exposure to a traumatic event. The exposure to trauma can evoke intense physical and emotional responses. Psychophysiological symptoms of PTSD can include an enhanced startle response; an effect that may result from an inability to inhibit fear. Conditioned fear can be measured using paradigms such as fear conditioning and fear extinction. Fear-potentiated startle is the process by which an individual's acoustic startle response is enhanced upon presentation of a conditioned stimulus (e.g., a colored shape) that was paired with an unpleasant unconditioned stimulus (e.g., an aversive airblast to the throat).

We have analyzed fear-processing in a population of PTSD patients from recent conflicts in the Middle East and healthy volunteers. One colored shape served as the reinforced conditioned stimulus (CS+, danger) and another colored shape served as the nonreinforced condition stimulus (CS-, safety). A 140 p.s.i airblast to the throat was used as the unconditioned stimulus. Subjects were fear-conditioned and, after a 10 minute interval, the subjects were trained to extinguish the fear. PTSD patients from the OIF theaters displayed greater fear-potentiated startle to the safety cue as well as delayed extinction of fear-potentiated startle in comparison to the healthy volunteers.

15. SUBJECT TERMS
Posttraumatic stress disorder (PTSD); fear conditioning; extinction; startle response

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Table of Contents

Section I: Introduction

This project represents an investigation of fear extinction and generalization in combat veterans returning from the theater of combat as part of the Global War on Terror (e.g., Operation Iraqi Freedom and Operation Enduring Freedom). We are studying fear processing in PTSD patients by examining (1) how well PTSD patients can *extinguish* learned fear and (2) the extent to which PTSD patients *generalize* their fear of specific trauma-related cues when exposed to similar cues. Reduced fear extinction and stimulus *over*-generalization may represent risk factors for PTSD and, as such, may still be present in PTSD patients and evident experimentally. A primary psychophysiological tool that we are using to assess fear extinction and stimulus generalization is *fear-potentiated startle* (FPS), or the relative increase in the amplitude of the acoustic startle response when a participant sees a signal that predicts the aversive stimulus used in this project. A third objective of this three-year study is to probe potential genetic biomarkers that govern one's resilience versus risk for developing PTSD following combat trauma. Using our established conditioned fear extinction paradigm (e.g., Norrholm et al., 2006), we are investigating potential candidate genetic polymorphisms underlying the vulnerability and symptomatology of PTSD. This translational study will focus on the contribution of genetic differences in PTSD patients and healthy control subjects to their individual ability to discriminate between danger and safety cues. In addition, this study will also examine the genetic contribution to the tendency for PTSD patients to over-generalize between danger cues and related stimuli (e.g., combat tones vs. environmental noises). In summary, an improved understanding of the genetic and epigenetic mechanisms that underlie the risk and symptoms associated with combat PTSD will enable clinicians to tailor treatment strategies according to the individual needs of each soldier returning from combat.

Section II: Body

Several major tasks at outlined in the approved Statement of Work have been accomplished in this period. The first milestone of preparing the research protocol and gaining approval from the Emory University Institutional Review Board and the Veterans Administration Research and Development Committee was completed in the first six months after initiation of funding. The second milestone of data collection for the fear acquisition and extinction task (Project Aim 1) was started immediately upon IRB approval and subject testing is taking place as scheduled. The third milestone of data collection for stimulus generalization (Project Aim 2) is proceeding ahead of schedule, as the task has already been developed and is being piloted on healthy volunteers, which was proposed to take place in the second year of the study.

Preparation of the Research Protocol

This task involved writing the research protocol and all required documentation, such as informed consent forms, and advertisements. The research study recruitment flyer was prepared by working closely with the VA Medical Media and is appended to this document. Prior to

submitting the protocol to IRB for approval, all personnel completed required training on human subjects' research. Upon completion of training the protocol was submitted to IRB and the study was approved in February of 2009.

Data Collection: Fear Acquisition and Fear Extinction Paradigm

This task involved recruiting, screening, clinically assessing and testing OIF/OEF veterans. The clinical assessments included diagnostic interviews in order to divide the veterans into groups according to their status: No PTSD diagnosis, PTSD diagnosis, or Depression diagnosis. The subjects were then tested using the psychophysiological methods described in the original funding proposal. The specific paradigm methods are described in more detail in the appendices. Briefly, fear-potentiated startle responses with electromyographic recordings of the eyeblink muscle was assessed using a colored shape as the reinforced conditioned stimulus (CS+, danger) and another colored shape as the nonreinforced condition stimulus (CS-, safety). A 140 p.s.i airblast to the throat served as the unconditioned stimulus. Subjects were fear-conditioned and, after a 10 minute interval, the subjects were trained to extinguish the fear. A trial-by-trial measure of awareness of reinforcement contingencies was collected via a response pad.

Forty-two subjects participated after signing an informed consent form approved by the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee. OIF veterans were referred to the study from the Trauma Recovery Program and related medical clinics at the Atlanta VAMC and healthy volunteers were recruited from the Emory University community. The 42 subjects were assessed and assigned to two groups: PTSD (n=12) and No PTSD (n=30).

Robust fear-potentiated startle to the danger cue (cue A) was displayed in both participants with and without PTSD (No PTSD: repeated measures (RM) ANOVA, main effect of Trial Type, $F(1,25)= 7.71$, $p=0.01$; PTSD: RM ANOVA, main effect of Trial Type, $F(1,9)=4.98$, $p=0.05$). There was no significant difference between the no PTSD and PTSD groups (RM ANOVA, no Block x Trial Type x Group interaction, $F(1,34)=0.003$, $p=0.96$).

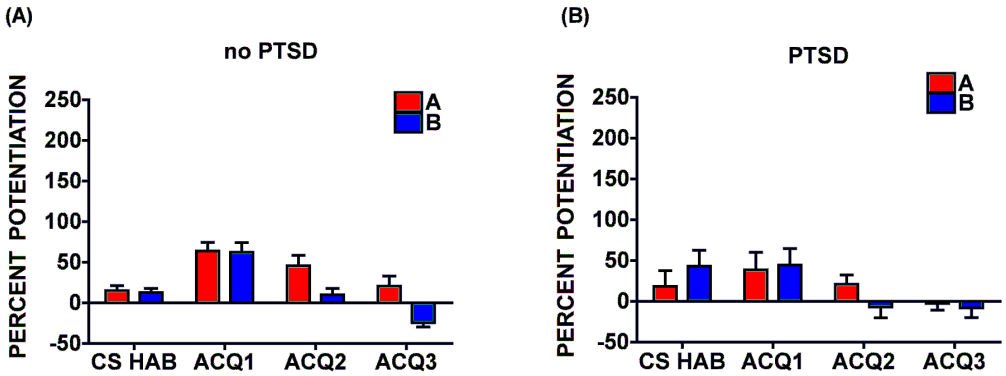

Figure 1. Fear-potentiated startle response to the danger (cue A) and safety (cue B) signals during the Fear Acquisition phase. Participants without PTSD and with PTSD displayed significant discrimination between the danger and safety cues.

Participants with and without PSD displayed significant discrimination between the danger (cue A) and safety (cue B) cues (No PTSD: repeated measures ANOVA, main effect of Trial Type, $F(1,25)=10.05$, $p=0.004$; PTSD: repeated measures ANOVA, main effect of Trial Type, $F(1,9)=5.09$, $p=0.05$, see Figure 1). There was no significant difference between the groups (RM ANOVA, no Block x Trial x Group interaction $F(1,34)=0.14$, $p=0.21$.

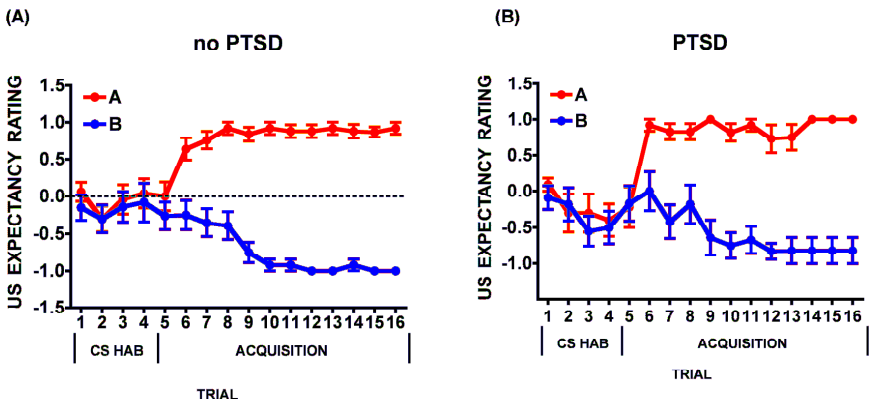

Figure 2. Contingency awareness during the Fear Acquisition session. Participants without PTSD and with PTSD correctly identified the danger (cue A) and safety (cue B) signals.

As shown in Figure 2, participants with and without PTSD correctly identified the Danger and Safety cues (No PTSD: repeated measures ANOVA, significant Trial x Trial Type interaction, $F(1,15)=354$, $p<0.01$; PTSD: repeated measures ANOVA, significant Trial x Trial Type interaction, $F(1,8)=34$, $p<0.01$). There was no significant difference between the groups (RM ANOVA, no Trial x Trial Type x Group interaction).

Participants with and without PTSD displayed robust fear-potentiated startle to the danger cue at the beginning of the Fear Extinction phase (No PTSD: RM ANOVA, main effect of Trial Type, $F(1,25)=20.74$, $p<0.01$; PTSD: RM ANOVA, main effect of Trial Type, $F(1,11)=8.82$, $p=0.01$, see Figure 3).

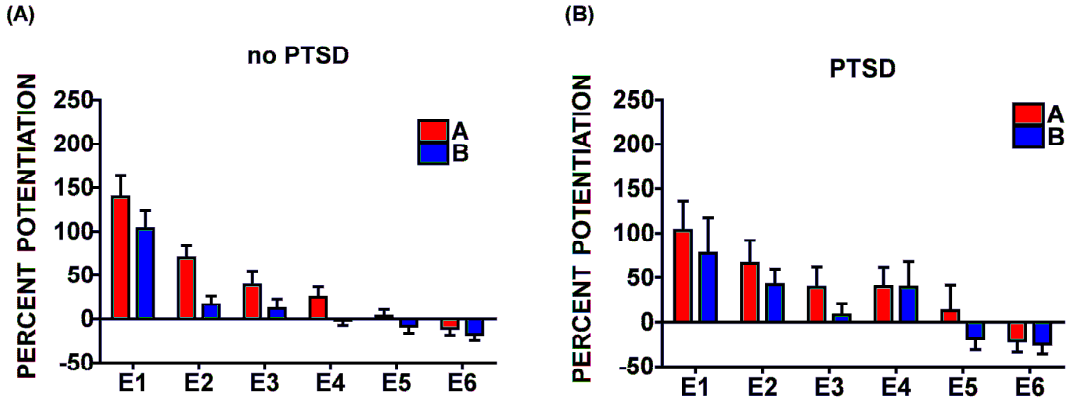

Figure 3. Participants without PTSD and with PTSD displayed a significant reduction in fear-potentiated startle during the Fear Extinction phase.

As shown in Figure 3, participants with and without PTSD displayed a significant reduction in fear-potentiated startle during the Fear Extinction phase (No PTSD: RM ANOVA, main effect of Block, $F(1,25)=45.1$, $p<0.01$; PTSD: RM ANOVA, main effect of Block, $F(1,11)=19.3$, $p<0.01$). Participants without PTSD showed significant discrimination between the danger and safety cues during the Fear Extinction (RM ANOVA, main effect of Trial Type, $F(1,25)=4.79$, $p=0.04$).

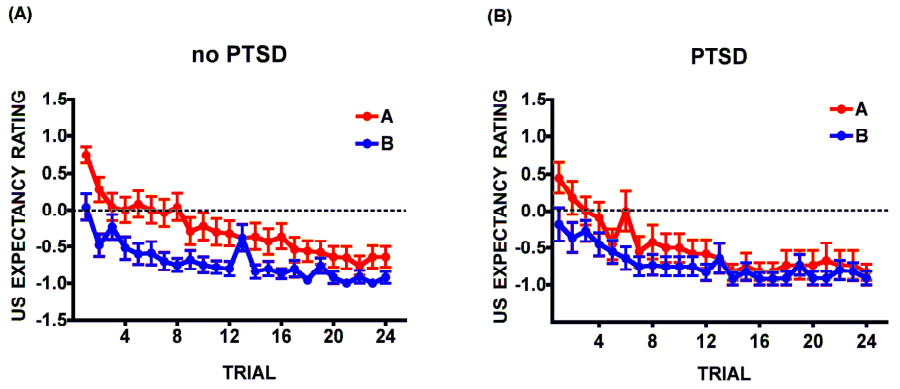

Figure 4. Contingency awareness during the Fear Extinction session. Participants without PTSD and with PTSD displayed a reduction in responses of danger on A trials.

As shown in Figure 4, Participants with and without PTSD displayed a reduction in responses of danger on A trials during the Fear Extinction phase (No PTSD: RM ANOVA, main effect of Trial $F(1,16)=37.5$, $p<0.01$; PTSD: RM ANOVA, main effect of Trial, $F(1,8)=13.76$, $p<0.01$).

Preliminary data illustrate delayed Fear Extinction in the PTSD group in the presence of both the previously reinforced A+ (danger) and the B- (safety, see Figure 5). Extinction Decrement was calculated by subtracting the mean startle response to each cue from the level of startle present in the beginning of Fear Extinction.

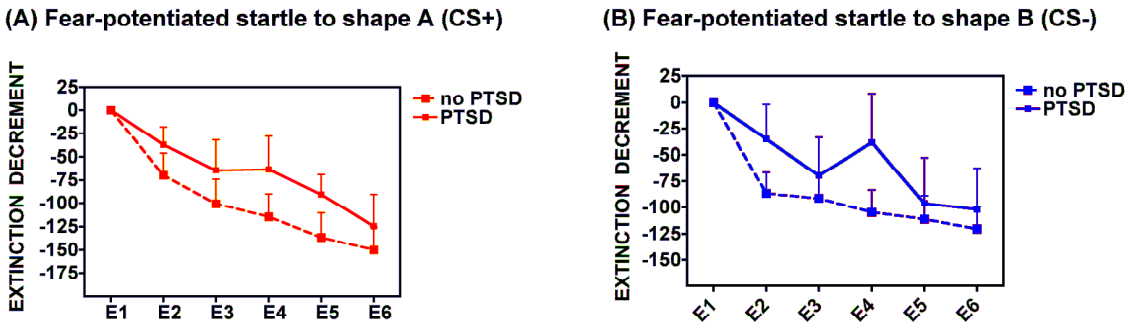

Figure 5. Preliminary data illustrate delayed Fear Extinction in the PTSD group in the presence of both the previously reinforced CS+ (shape A) and the CS- (shape B). Extinction Decrement was calculated by subtracting the mean startle response to each cue from the level of startle present at the beginning of Fear Extinction.

The present research report summarizes preliminary data collected as part of an ongoing investigation. These findings show that PTSD patients from the OIF theaters of conflict: (1)

acquire conditioned fear similar to controls, (2) are able to correctly identify danger and safety cues during Fear Acquisition, (3) extinguish fear at an apparent slower rate on danger and safety trials during Fear Extinction in a manner that is different from control subjects, and (4) showed less discrimination on US-expectancy ratings between the Danger (cue A) and Safety (cue B) signals during Fear Extinction. The results of the current study are consistent with previous results from this laboratory with regard to the Acquisition and Extinction of conditioned fear in healthy controls (Norrholm *et al.*, 2006; Jovanovic *et al.*, 2009). The present study is the first to use this paradigm to assess fear processing in combat PTSD patients. The data support our hypothesis that fear extinction would be impaired in PTSD patients.

The results of the present study are consistent with an increasing number of investigations that have found deficits in safety signal processing associated with PTSD (Peri *et al.*, 2000; Bremner *et al.*, 2005; Blechert *et al.*, 2007; Wessa and Flor, 2007; Milad *et al.*, 2008; Jovanovic *et al.*, 2009; Lissek *et al.*, 2009). A small number of prospective studies suggest that impaired suppression of fear during extinction may be a risk factor for PTSD (Guthrie and Bryant, 2006; Pole *et al.*, 2009). While cognitive measures of safety signal learning parallel the physiological findings in some studies (Blechert *et al.*, 2007; Lissek *et al.*, 2009), our results show a dissociation between cognitive awareness of safety and startle potentiation, in that PTSD subjects were aware that they would not receive the aversive airblast but still showed heightened responding to the CS-.

Data Collection: Stimulus Generalization Paradigm

This task involved developing a new fear-potentiated startle paradigm in which the conditioned stimuli were auditory rather than visual cues. The psychophysiological data recording methods were the same as described above, using the EMG of the startle response. The auditory cues were selected from a range of pure tones (250, 500, 1000, 2000, 4000, 6000, 8000 Hz). Subjects were differentially conditioned to the highest and lowest tones such that trials containing the 8000 Hz tone (CS+) were reinforced with an airblast while tones at 250 Hz were not reinforced (CS-). This allows us to examine the ability of PTSD patients to inhibit fear to the nonreinforced cue (CS-) as well as the extent to which their fear is generalized to tones that are similar in frequency to the reinforced cue (8000 Hz, CS+).

Figure 6 shows data from a pilot subject on this paradigm. During Acquisition, this subject showed robust fear-potentiated startle to the CS+, expressed as Difference Score from baseline, and clear discrimination between the CS+ and CS-. Difference score = Startle magnitude in response to the CS – Startle Magnitude to the noise probe alone (baseline). During the Generalization test, this participant displayed greater responding, as measured by fear-potentiated startle, to the previously reinforced CS+ as compared to the CS-. In addition, the subject showed a heightened startle response to the tones that were closest in frequency (e.g., 250 Hz and 1000 Hz) to the CS+ and less responding to the tones that were closest in frequency (e.g., 2000 Hz and 8000Hz) to the CS-.

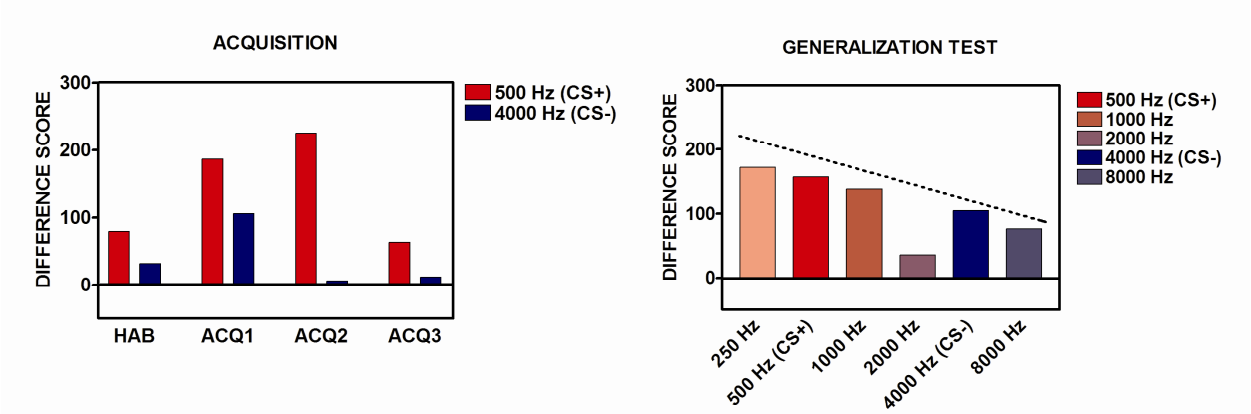

Figure 6. Representative graph from a single case depicting fear acquisition and stimulus generalization as part of Specific Aim 2 of the current study. The conditioned stimuli for this Aim are 4 second tones of 500 Hz (CS+) and 4000 Hz (CS-). The dotted line illustrates a hypothetical generalization gradient of fear-potentiated startle responses to tones within the test range (250 – 8000 Hz).

These data demonstrate the utility of stimulus generalization as a psychophysiological tool. This is a novel technique that has not been understudied in humans, but has the potential to contribute to our understanding on PTSD symptoms with regard to generalization of fear responses.

Section III: Key Research Accomplishments

- **Research protocol written and approved by Emory IRB, VA R&D Committee, and USAMRMC HRPO**
- **Recruitment flyers and brochure generated and approved by Emory IRB and VA R&D**
- **42 participants recruited, screened, and enrolled into the study from the date of protocol approval by HRPO in February 2009 until July 2009.**
- **US Army Reservist completed rotation in lab as part of the Atlanta Center for Behavioral Neuroscience BRAIN program**
- **Trained research assistants to work on all phases of the study protocol**
- **Presented research findings at local and international conferences (see next section)**

Section IV: Reportable Outcomes

Abstracts

Jones, M., Jovanovic, T., Olin, I., Daugherty, M., Skelton, K., Duncan, E., Bradley, B., & **Norrholm, S.D.** (2009). Conditioned fear acquisition, discrimination, and extinction in combat veterans from Operation Iraqi Freedom (OIF) with posttraumatic stress disorder (PTSD). Center for Behavioral Neuroscience (CBN) Summer Research Symposium, Atlanta, GA.

Leimbach, L.B., Daugherty, M.D., Russ, E., Crowe, C., Skelton, K., Jovanovic, T., Ressler, K., Duncan, E, Bradley, B., & **Norrholm, S.D.** (2009). Conditioned fear acquisition, discrimination, and extinction in combat veterans from Operation Iraqi Freedom (OIF) with posttraumatic stress disorder (PTSD). Georgia/South Carolina Neuroscience Consortium Annual Meeting, Athens, GA.

Daugherty, M.D., Leimbach, L.B., Russ, E., Crowe, C., Skelton, K., **Norrholm, S.D.** & Bradley, B. (2009). OIF/OEF veterans with post-traumatic stress disorder: A first look. Georgia/South Carolina Neuroscience Consortium Annual Meeting, Athens, GA.

Presentations

Norrholm, S., Jovanovic, T., Rothbaum, B., Davis, M., Bradley, B., Ressler, K., & Duncan, E. (May 2009). Translational approaches for the study of risk and resilience for PTSD following trauma exposure. 21st Annual meeting of the Association for Psychological Science, San Francisco, CA.

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Section V: Conclusion

The current study provides further validation for Fear Acquisition, Extinction and Stimulus Generalization paradigms to be used as an assessment tool for fear processing in PTSD. The paradigms allow us to detect both physiological and cognitive measures of learned fear and extinguished fear, as well as generalization of danger cues. The goal of many exposure therapies (which are similar to extinction training) is to facilitate the extinction of fear acquired during combat exposure. This fear potentiated startle paradigm may prove useful for assessing the ability to extinguish learned fear both before and after exposure therapy.

Based on the data collected this far, we plan to continue as proposed in the original Statement of Work.

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Pole, N., Neylan, T. C., Otte, C., Henn-Hasse, C., Metzler, T. J., and Marmar, C. R. (**2009**). "Prospective Prediction of Posttraumatic Stress Disorder Symptoms Using Fear Potentiated Auditory Startle Responses," Biological Psychiatry **65**, 235-240.

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Section VI: Appendices

Study Brochure

Participant Recruitment Flyer

Department of Veterans Affairs

Informed Consent to be Contacted by Research Staff:

_____

Veteran's Name

_____

Veteran's Signature Date

_____

Referring Clinician

_____

Are you a veteran of Operation Enduring Freedom (OEF) or Operation Iraqi Freedom (OIF)? _____ Yes _____No

May we contact you about participation in VAMC sponsored clinical research (please initial)?

_____ _____

Yes No

Contact address:

Contact phone number:

Brochure approval date:

Emory IRB _____

VA R&D _____

Helpful Resource

National Center for PTSD

www.ncptsd.gov

Atlanta VA Medical Center

Patient Centered Care...Second to None...One Veteran at a Time

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Department of Veterans Affairs

Please Support VA Research

Trauma Recovery Program

Atlanta VA Medical Center

Patient Centered Care...Second to None...One Veteran at a Time

Following deployment to the current conflicts in Iraq and Afghanistan, and as a result of U.S. presence in other conflicts over the last 30+ years, an unprecedented number of veterans are at risk for PTSD and other chronic mental health problems. These problems can follow exposure to the stress and trauma of war-zone experiences and can affect thousands of veterans; many of whom may develop severe symptoms that can last several years or more if not properly treated. With this in mind, it is imperative that we here at the Atlanta VAMC develop the best possible treatments for these veterans and their families. Clinical research is a critical element of this mission.

The research we conduct here helps us provide better care to our veterans. Partnering with researchers from the Emory University School of Medicine, the Atlanta Veteran's Administration Medical Center's Trauma Recovery Program (TRP) seeks to provide the best available, state of the art, mental health care to veterans. We specialize in addressing the symptoms of PTSD and other psychological conditions that can result from combat-related traumatic experiences. Our goal at the TRP is to do our best to insure that veterans recover from the psychological impact of trauma.

Your participation in TRP Research aids us tremendously in our effort to provide better care and support to all veterans. Just as thousands of research participants have made current therapies possible, your participation in clinical research will provide information for the betterment and advancement of medical care for future generations. Participation in this research is optional and your decision to participate (or not) does not in any way impact your VA health care or benefits.

Trauma Recovery Program Staff serving your needs here at the Veteran's Administration Medical Center are:

BEKH BRADLEY, Ph.D.
(Clinical Community Psychology, University of South Carolina, 2000) is the Director of the Atlanta VAMC Trauma Recovery Program. Dr. Bradley's primary clinical and research interests are in the areas of risk and resilience factors for developing PTSD as well as PTSD treatment process and outcome.

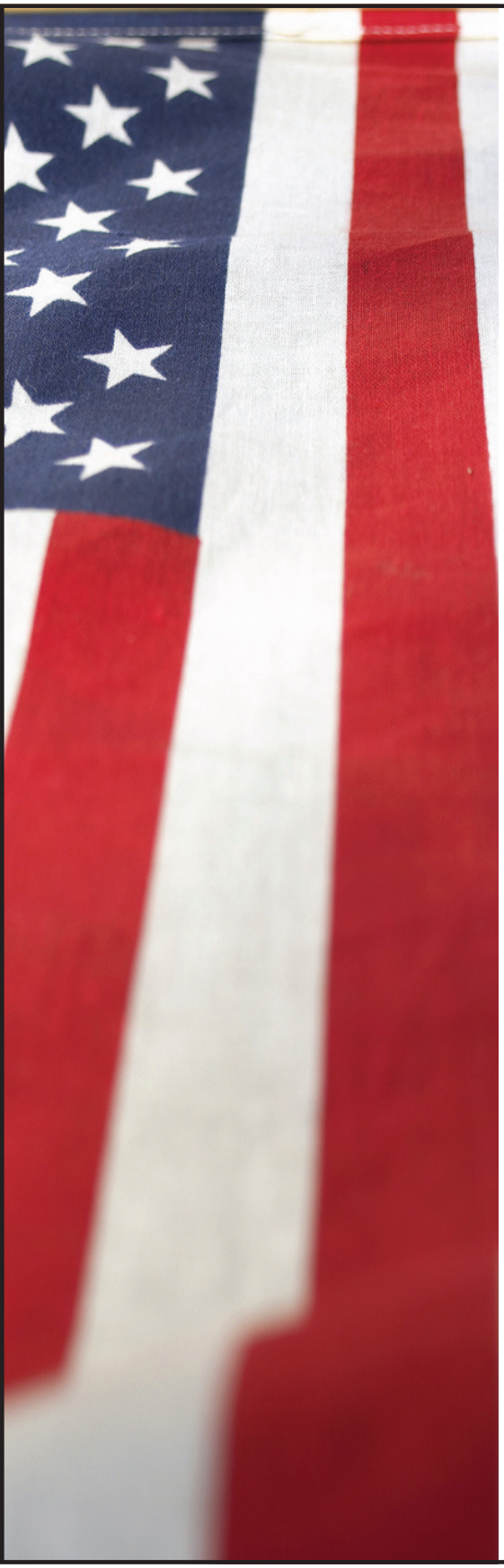
KELLY SKELTON, M.D., Ph.D.
(Emory University School of Medicine, 2002) is a psychiatrist and Medical Director of the Trauma Recovery Program. She has a background in studies of stress neurobiology in animal models, as well as clinical research focusing on the biological foundation of PTSD. Her clinical work involves the treatment of PTSD in the veteran population through the use of both psychotherapy and medication.

CHRIS M. CROWE, Ph.D.
(Clinical Community Psychology,
University of South Carolina, 1989) is a cognitive behavioral psychologist working with the Trauma Recovery Program, coordinating programs for OEF and OIF veterans. His clinical interests include cognitive behavioral treatment of the anxiety disorders in general and PTSD in particular. His research interests include exposure therapies, virtual reality, co-morbid PTSD and traumatic brain injury, and the role anxiety sensitivity may play in the development and maintenance of PTSD.

MIKYTA DAUGHERTY, Ph. D. (Clinical Psychology, University of New Mexico, 2007) is a post doctoral fellow who works with the Trauma Recovery Program's clinical and research teams. Her interests include the use of exposure and cognitive processing treatment models for patients with PTSD and co-morbid disorders.

For information regarding study participation contact:
Seth Norrholm at (404) 321-6111 ext. 5887

SETH D. NORRHOLM, Ph.D.
(Neuroscience, Florida State University, 2001) is the Program Evaluation Coordinator for the Trauma Recovery Program at the Atlanta VAMC and an Assistant Professor of Psychiatry in the Emory University School of Medicine. Using cutting edge translational research methods, he hopes to assist in developing improved treatment strategies for PTSD.



PTSD and/or Major Depression?

Emory University and the **Atlanta VA Medical Center** are currently recruiting participants for a research study on **PTSD** and **major depression**. We are currently seeking individuals who meet the following criteria:

- **Veterans diagnosed with PTSD and/or major depression who served in Operation Enduring Freedom (OEF) and/or Operation Iraqi Freedom (OIF)**
- **Veterans who served in OEF and/or OIF who DO NOT have PTSD or major depression**
- **Civilians (non-veterans) with major depression**
- **Healthy civilian controls (no diagnosable psychiatric disorders)**

* **Participants must be between the ages of 18 and 65, and have no signifi cant hearing or non-correctable vision loss, no loss of consciousness last ing longer than 5 minutes, no HIV/AIDS, and no current drug or alcohol abuse problems.**

Participation lasts 5-7 hours spread over 2-3 consecutive days, and may involve a brief pre-screening interview, a hearing test, a urine test for illicit drug use, physiological testing, and medical/psychiatric history interviews. This study **DOES NOT involve medication**. All eligible participants receive $30 per day compensation for up to 3 days' participation.

For more information, contact **Dr. Seth Norrholm** at **(404) 321-6111 ext. 5887**.